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PHASE FOUR REVIEW

(NOTE: This only contains additions and changes from the phase 2 response)

Pesticide: Pirimiphos methyl Chem.#/Case#: 108102/2535
Transmitted to HED on November 19,1990
Tox. Chem.#: 334B .
Sponsor: ICI Americas, Inc.
CRM: Jay Ellenberger Phone #: 308-8085

Branch: Toxicology I, Section II Reviewer: M. Morrow, D.V.M.
Completed: _____ Concurrence: Signature 12/21/90

Response by Guideline

Guideline #: 81-1 **Description:** Acute oral/rat
MRID #: 92147-006, **Study #:** CR1970
Discussion/ Recommendation: The sponsor has requested a waiver for conducting a study with the technical grade active ingredient (TGAI). It is their contention that the 75.4% product is more readily available in the alimentary tract because of the emulsifying agents and that this property would represent a worst case scenario with regard to the acute oral toxicity of the compound. The sponsor has provided a summary of a study conducted with a 40% formulation. This is a data gap since a summary was not provided for the 75% formulation.

Guideline #: 81-2 **Description:** Acute dermal/rat
MRID #: 92147-007, **Study #:** CR1970
Discussion/Recommendation: The sponsor has requested a waiver of this study based on the reasons provided for study 81-1. The case made for the waiver of the oral study would not apply to other routes of administration; therefore, a waiver of the acute dermal can not be granted. This is a data gap.

Guideline #: 81-3 **Description:** Acute inh/ rat
MRID #: 415563044, **Study #:** CTL/P/2795
Discussion/ Recommendation: This study is acceptable for review. The only deviation from the acceptability criteria was that the relative humidity ranged from 25 to 40%. This deviation is not enough to invalidate the study.

Guideline #: 81-4 **Description:** Primary eye Irr./rabbit
MRID #: 92147-008, **Study #:** FB3241
Discussion/Recommendation: A study is still needed for the technical product (this study used a 40% formulation). The rationale used to support the waiver of an acute oral study can not be used to waive this study. A study conducted with the technical product is required. This is a data gap.

Guideline #: 81-5 **Description:** 1° Derm. Irr/ rabbit
MRID #: 92147-009, **Study #:** EBZ700
Discussion/ Recommendation: The TGAI was not tested . A waiver was requested based on the reasons stated under 81-1. This rationale for a waiver would not apply for the dermal irritation study. A study conducted with the TGAI is required. This is a data gap.

Guideline #: 81-6 **Description:** Dermal sens./Guinea pig
MRID #: 92147-010 and 92417-011, **Study #:** GG3201 and GG0405
Discussion/ Recommendation: The first study referenced above did not use the TGAI, but a 40% formulation. Neither study was conducted using a positive control;however, a separately reported positive control study was used to evaluate the results obtained in both studies. The study is unacceptable since a concurrent positive control is required. This is a data gap.

Guideline #: 81-7 **Description:** Acute Del Neuro/Hen
MRID #: 415995-03, **Study #:** CTL/C/2167
Discussion/Recommendation: A study was provided even though the requirement was waived by the agency in Phase II based on the fact that the sponsor had conducted a 90 day neurotoxicity in hens. (See 82-5).

Guideline #: 82-2 **Description:** Repeat dose Dermal/rabbit
MRID #: 92147-012, **Study #:** 38/59
Discussion/Recommendation: The following deviations from the acceptance criteria were noted: Blood samples were not taken at the termination of the study, but rather on day 17 or 18. Creatinine phosphokinase, creatine and inorganic phosphorous were not measured and a urinalysis was not performed. It felt that these deviations will not adversely affect the validity of the study.

Guideline #: 82-5 **Description:** Subchr. (90day) Neuro/Hen
MRID #: 92147-013, **Study #:** CTL/C/1200
Discussion/Recommendation: The only deviation from the acceptance criteria was the examination of the distal rather than the proximal branch of the tibial nerve. This will not affect the validity of the study; therefore it is acceptable for review.

Guideline #: 83-1(a) **Description:** Chronic rodent
Discussion/Recommendation: See 83-5

Guideline #: 83-1(b) **Description:** Chronic(2 year) Tox/dog
MRID #: 92147-014 **Study #:** CTL/C/246

Discussion/ Recommendation: Deviations from the acceptance criteria included failure to collect all required clinical chemistry data (AST, LDH, inorganic phosphorous, calcium); failure to collect all required data from urinalysis (blood, total bilirubin); failure to record the appearance of the urine and failure to conduct histopath on the cecum, oviduct and the rectum. The sponsor states that the tests that were carried out were sufficient to evaluate liver and kidney function. The study is acceptable for review.

Guideline #: 83-2(a) **Description:** Oncogenicity/Rat

Discussion/Recommendation: See 83-5

Guideline #: 83-2(b) **Description:** Oncogenicity/mouse
MRID #: 92147-015, **Study #:** CTL/C/340

Discussion/Recommendation: A NOEL was not determined for systemic toxicity; however, this is a supplemental criteria and would not affect the acceptability of the study. Histopathology was only conducted on those organs which showed gross lesions and no organ weights were measured. The sponsor states that geriatric pathological changes would lead to a variation of organ weights and that organ weight measurement would not affect information on carcinogenicity.

It is felt that in the absence of complete histopathology and with the failure to measure organ weights the study is unacceptable and this is a data gap.

Guideline #: 83-3(a) **Description:** Teratology/ rat
MRID #: 92147-016, **Study #:** RR0292

Discussion/ Recommendation: The study is acceptable for review.

Guideline #: 83-3(b) **Description:** Develop. Tox/ rabbit
MRID #: 92147-017, **Study #:** RB0018

Discussion/Recommendation: The number of pregnant rabbits was fewer than 12 and only two test groups were used. Maternal toxicity was demonstrated in these animals . Food consumption was not measured; however the test material was not administered in the diet. Additionally, only half of the fetuses were examined for skeletal abnormalities and the other half were examined for visceral abnormalities. The study is unacceptable for review.

Guideline #: 83-4 **Description:** 2- Gener. Repro/rat
MRID #: 92147-018, **Study #:** CTL/C/242 and CTL/C/339

Discussion/Recommendation: This combined study contains too many deviations from the acceptance criteria to be considered for acceptable for review. Among the noted defiencies are failure to allow for 20 pregnant animals per dose group; failure to conduct histopath of the reproductive organs in high dose and control P_1 and F_1 animals; failure to conduct daily observations. In addition to these the mating ratio was 1 male:2 females; the ages of the P_1 animals were not given. Toxicity was reported at the HDT in one study, but the specific parameter used to determine toxicity was not measured at the HDT in the second study. (Data gap).

Guideline #: 83-5 **Description:** Chronic feeding/Onco/rat
MRID #: 92147-019, **Study #:** PR0045

Discussion/Recommendation: Deviations from the acceptance criteria included the use of 48 male and 48 female animals instead of the recommended 50; clinical chemistry conducted on 8 rather than 10 animals/sex/group; no urinalysis conducted; necropsies not performed on all animals because some were found dead and had varying degrees of autolysis; testes and brain were not weighed; and not all tissues were examined histologically (aorta, esophagus, muscle, skin, lymph node, mammary gland, eyes, oviduct and rectum) unless there were gross abnormalities present.

This study is acceptable for review and it is not considered a data gap at this time.

Guideline #: 84-2(a) **Description:** Salm. typhim. gene mut. assay
MRID #: 92147-020 , **Study #:** YV1226

Discussion/ Recommendation: Acceptable for review.

Guideline #: 84-2(b) **Description:** Muta-Dominant Lethal/Mouse
MRID #: 41556302, **Study #:** CTL/C/291

Discussion/Recommendation: Major deficiencies in the response would render this study unacceptable. Deficiencies include failure to test technical, no detail of animal care/husbandry, no indication whether HDT was toxic.

Guideline #: 84-2 **Description:** Gene mutation/Mammalian cells
MRID #: 41556303, **Study #:** CTL/C/1437

Discussion/Recommendation: The study is acceptable for review.

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R111374

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